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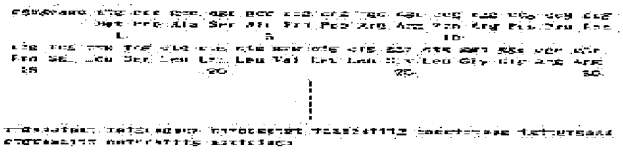
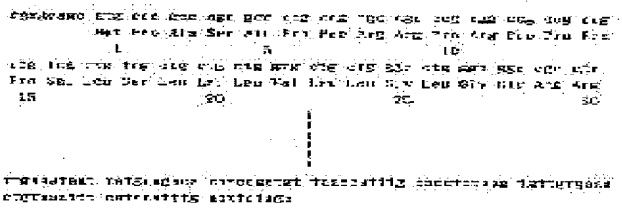
(54) NEW CAPILLARY ENDOTHELIAL FUNCTION IMPROVEMENT

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a medicinal composition that can ameliorate the morbid states of capillary endothelial function, hypertension and arteriosclerosis in an animal model onset the diseases



accompanied by deterioration in capillary endothelial function by incorporating the recombinant vector incorporating the klotho gene.
SOLUTION: The objective medicinal composition includes an effective amount of a recombinant vector incorporating the cDNA of the klotho gene. In a preferred embodiment, the cDNA of the klotho gene is a DNA having the base sequence selected from the base sequence of the formula or the like or another DNA that can hybridize with the DNA under the stringent conditions. The recombinant vector is preferably prepared by incorporating the cDNA of the klotho gene into a vector selected from-plasmid vectors or a virus vectors. The resultant medicinal composition is useful for amelioration or prophylaxis of the morbid states caused by the morbid states of capillary endothelial function (for example, hypertension and arteriosclerosis in an animal model onset the diseases accompanied by deterioration in capillary endothelial function.



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CLAIMS

[Claim(s)]
[Claim 1] The remedy constituent for improving or preventing the symptoms by blood vessel inner-bark functional degradation of the mammalian incorporating the KUROSO gene cDNA which rearranges and comes to contain the effective dose of a vector.
[Claim 2] The remedy constituent according to claim 1 whose KUROSO gene cDNA is the aging inhibitor cDNA given in WO 98/29544.
[Claim 3] The remedy constituent according to claim 1 which is DNA which has the base sequence as which the KUROSO gene cDNA is chosen from the base sequence expressed with the array numbers 1, 2, 3, 4, and 5, or this DNA and DNA hybridized under stringent conditions.
[Claim 4] The remedy constituent according to claim 1 whose symptoms by blood vessel inner-bark functional degradation are the diseases chosen from the group which consists of hypertension, arteriosclerosis, hypercholesterolemia, diabetes mellitus, myocardial infarction, and cerebral infarction.
[Claim 5] The remedy constituent according to claim 1 with which a recombination vector includes the KUROSO gene cDNA in the vector chosen from a plasmid vector and a virus vector.
[Claim 6] The remedy constituent according to claim 1 with which a virus vector is chosen from a retrovirus vector, an adenovirus vector, an adeno-associated virus vector, and a Herpes virus vector.
[Claim 7] The KUROSO gene recombination vector which included the KUROSO gene cDNA in the virus vector.
[Claim 8] The KUROSO gene recombination vector according to claim 7 as which a virus vector is chosen from a retrovirus vector, an adenovirus vector, an adeno-associated virus vector, and a Herpes virus vector.
[Claim 9] How to perform the therapy or prevention of these symptoms by medicating with the effective dose the mammalian which may lapse into

mammalian with symptoms according a remedy constituent according to claim 1 to 6 to blood vessel inner-bark functional degradation, or these symptoms.

[Claim 10] The approach according to claim 9 the symptoms by blood vessel inner-bark functional degradation are the diseases chosen from the group which consists of hypertension, arteriosclerosis, hypercholesterolemia, diabetes mellitus, myocardial infarction, and cerebral infarction.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the recombination vector which uses lapsing the symptoms by blood vessel inner-bark functional degradation into an improvement or its condition for the approach for preventing, a remedy constituent, and them. It is related with the recombination vector used for the remedy constituent and them which are used more for the approach of medicating the mammalian which may lapse into these symptoms or it has these symptoms with the expression vector which contains in a detail the gene DNA for the blood vessel inner-bark functional improvement represented by the KUROSO gene, and preventing lapsing these symptoms into an improvement (therapy) or its condition, and this approach.
[0002]
[Description of the Prior Art] A KUROSO gene is a gene identified as a gene of cause which causes the shape of said aging to a mouse, when it exists in the foreign gene insertion section of the transgenic mouse (KUROSO mouse) which presents remarkable and variegated premature-aging symptoms, such as withering of compaction of a life, mineralization of various organs, arteriosclerosis, and a reproduction organ, and the manifestation falls. After that, growth stops and a KUROSO mouse shows the indication of various aging, although it grows like [the 3rd week of after the birth] the mouse of a wild type. If it becomes 6 weeks old, the activity of a KUROSO mouse will fall to about 50% of a wild type, and a walk of the Parkinson's disease will be seen. Gonad has shrunk and is sterility. Osteoporosis becomes remarkable and also mineralization of the heterotopia arises in the choroid plexus of an aortic valve, a bronchial tube, and a brain. An arterial system shows the arteriosclerosis opinion of a MENKEBERUGU mold characteristic of aging, such as thickening of blood vessel intima, and mineralization of a media. In

addition, withering of the skin and versicular emphysema also come to be observed [WO 98/29544, Nature, 390, and 45 (1997)]. From the analysis of cDNA of a KUROSO gene, two kinds of mRNA(s) are imprinted by the difference in splicing, and, as for a KUROSO gene, two kinds of proteins are translated from this mRNA (the proteins including these proteins by which a code is carried out to a KUROSO gene are hereafter called KUROSO protein).

[0003] One protein is 1 type film protein (it is hereafter called film joint mold KUROSO protein) with the structure of having the signal sequence field of an amino terminal, an extracellular domain field, and the film penetration domain field of a C terminal, among the KUROSO proteins by which a code is carried out to the two above-mentioned kinds of mRNA(s), and the extracellular domain consists of two domains (KL1, KL2) which have homology in the beta-glucosidase of bacteria or vegetation. On the other hand, it was shown clearly that another protein was a secretory protein (it is hereafter called secretor KUROSO protein) which has the signal sequence field of an amino terminal and KL1 domain field [Biochem.Biophys.Res.Commun., 242, and 626 (1998)].

[0004] Neither the mechanism which KUROSO gene variation causes the shape of various aging, nor the molecule function of KUROSO protein is clarified yet. Although KUROSO gene expression is high with the kidney, the shape of intense aging has attained to the whole body organ containing lungs, a bone, stomach walls, the skin, etc. A certain secretory factor existing in the molecule function, and demonstrating the operation from this, is presumed [Nature, 390, and 45 (1997)].

[0005] By the hybridization experiment of a KUROSO mouse and a KUROSO gene expression transgenic mouse, the experiment which makes KUROSO protein discover in a KUROSO mouse body using the adenovirus vector incorporating cDNA of a film joint mold KUROSO gene Since prevention of the aging-like onset of a KUROSO mouse was attained, the therapy of the disease originating in the malfunction of KUROSO protein Being attained by reinforcing a KUROSO gene using a certain means is suggested [Nature, 390, 45 (1997), and WO 98/29544]. A vascular endothelial cell emits an inner-bark dependency blood vessel relaxing factor and an inner-bark dependency vasoconstrictor, is participating also in the permeability of blood vessel intima, or platelet aggregation deeply, and it not only is adjusting the vasotonia, but it is playing the role important for onset progress of a thrombus nature condition pulse disease. As a blood vessel inner-bark dependency blood vessel relaxing factor, a nitrogen monoxide (NO), a prostagladin I2, C mold natriuresis peptide, adrenomedullin, a blood vessel inner-bark origin hyperpolarization factor, etc. are mentioned. On the other hand, as an inner-bark dependency vasoconstrictor, thromboxane A2,

angiotensin II, endothelin, and prostaglandin H 2 grade are known.
[0006] When NO made acetylcholine act on the extraction sample which is a rabbit artery, it was identified from arising [the relaxation response]-specifically [Nature and 288:373(1980)] only by the sample holding an endothelial cell as one of the blood vessel inner-bark origin blood vessel relaxing factors (EDRF). The NO synthase (NOS) which exists in a blood vessel inner bark oxidizes L-arginine, and NO separates. NO reaches the adjoining blood vessel smooth muscle cell, activates the guanylate cyclase, makes cGMP increase, and results in blood vessel relaxation. Existence of three kinds of isoforms, the nerve mold NOS (nNOS), the inner-bark mold NOS (eNOS), and an induction type NOS (iNOS), is clarified at NOS. Among these, with the deficit mouse of the inner-bark mold NOS, since the vasodilatation reaction of an inner-bark dependency was lacked and blood pressure also became high 20 mmHgs from the healthy mouse, it was shown that the vasoconstriction regulatory mechanism of indispensable NO dependency exists in accommodation of a blood flow or blood pressure [Nature, 377, and 239 (1995)].
[0007] Thus, it is an important problem on clinical for close relation between a blood vessel inner-bark function and the amount of NO(s) which an endothelial cell produces to be, and to measure the production ability of NO. However, the attempt in which it will measure NO directly since only a minute amount exists and also NO is unstable is not applied to a clinical field. Consequently, the moving state of NO is presumed by generally measuring the function of a blood vessel inner bark. The function of a blood vessel inner bark is performed by generally investigating the vasodilatation reaction of an inner-bark dependency [****** 189 of medicine and 517 (1999)]. This is the approach medicate an artery with an inner-bark dependency vasodilator like acetylcholine, and extent of the vasodilatation in that case estimates NO secretion ability of an inner bark. In a KUROSO mouse, if the blood vessel inner-bark dependency relaxation response [as opposed to acetylcholine for a blood vessel inner-bark function] is measured against an index, compared with a normal mouse with high KUROSO gene expression, the maximum vasodilatation reaction will fall in the artery of a KUROSO mouse. Moreover, with the KUROSO hetero mouse with which KUROSO gene expression is falling to abbreviation one half compared with a normal mouse, although the maximum vasodilatation reaction is not a KUROSO mouse, since it is falling, it is suggested between the amount of KUROSO gene expression, and the function of a blood vessel inner bark that there is correlation. It is shown in the blood vessel functional disorder in a KUROSO mouse that NO production failure in a vascular endothelial cell is concerned [BBRC, 248, and 324 (1998)]. [BBRC, 248, and 324] which the function of the blood vessel inner bark of a KUROSO hetero mouse will recover even to same extent as a

normal mouse if a normal mouse and a KUROSO hetero mouse individual are combined by surgical operation and exchange of body fluid is actually made to be performed among both (1998) -- enhancement of KUROSO protein expects from things that a blood vessel inner-bark function will be improvable. However, there is no report that a KUROSO gene or KUROSO protein was prescribed for the patient and the therapy or prevention of such a disease was performed from the exterior in the disease to which the blood vessel inner-bark function fell, for example, diseases, such as arteriosclerosis and hypertension.

[0008]

[Problem(s) to be Solved by the Invention] The origin of symptoms, such as hypertension and arteriosclerosis, is complicated, and development of a remedy and preventive based on a new operation mechanism is desired so that a cure can be chosen according to a patient's symptoms and complication.

[0009]

[Means for Solving the Problem] It came to complete header this invention for the symptoms of the blood vessel inner-bark function of those animals used in disease modeling, hypertension, and arteriosclerosis being improvable to the animal model which showed the symptoms of diseases accompanied by lowering of a blood vessel inner-bark function, such as hypertension and arteriosclerosis, by [incorporating the KUROSO gene cDNA] rearranging and prescribing a vector for the patient.

[0010] The invention in this application relates to following the (1) - (10).

(1) The remedy constituent for improving or preventing the symptoms by blood vessel inner-bark functional degradation of the mammalian incorporating the KUROSO gene cDNA which rearranges and comes to contain the effective dose of a vector.

(2) The remedy constituent given in 1 term the given KUROSO gene cDNA is the aging inhibitor cDNA given in WO 98/29544.

(3) The remedy constituent given in one which is DNA which has the base sequence as which the KUROSO gene cDNA is chosen from the base sequence expressed with the array numbers 1, 2, 3, 4, and 5, or this DNA and DNA hybridized under stringent conditions.

(4) The remedy constituent given in 1 term the given symptoms by blood vessel inner-bark functional degradation are the diseases chosen from the group which consists of hypertension, arteriosclerosis, hypercholesterolemia, diabetes mellitus, myocardial infarction, and cerebral infarction.

(5) The remedy constituent given in 1 term with which a recombination vector includes the KUROSO gene cDNA in the vector chosen from a plasmid vector and a virus vector.

(6) The remedy constituent given in 1 term with which a virus vector is

chosen from a retrovirus vector, an adenovirus vector, an adeno-associated virus vector, and a Herpes virus vector.
(7) The KUROSO gene recombination vector which included the KUROSO gene cDNA in the virus vector.
(8) The KUROSO gene recombination vector given in 7 terms as which a virus vector is chosen from a retrovirus vector, an adenovirus vector, an adeno-associated virus vector, and a Herpes virus vector.
(9) How to perform the therapy or prevention of these symptoms by medicating with the effective dose the mammalian which may lapse into the mammalian which has symptoms according the remedy constituent of a publication to blood vessel inner-bark functional degradation in either of one to 6 terms, or these symptoms.
(10) The approach given in 9 terms the symptoms by blood vessel inner-bark functional degradation are the diseases chosen from the group which consists of hypertension, arteriosclerosis, hypercholesterolemia, diabetes mellitus, myocardial infarction, and cerebral infarction.
[0011]
[Embodiment of the Invention] According to this invention, the therapy or prevention of these symptoms can be performed by medicating the mammalian which may lapse into mammalian with symptoms according the remedy constituent for improving or preventing the symptoms by blood vessel inner-bark functional degradation incorporating the KUROSO gene cDNA of the mammalian which rearranges and comes to contain the effective dose of a vector, for example, hypertension, and arteriosclerosis to blood vessel inner-bark functional degradation, or these symptoms.
[0012] A recombination vector can be obtained by including the KUROSO gene cDNA in a vector. Although a plasmid vector or the vector (virus vector) of a virus can be used, in order to introduce the KUROSO gene cDNA into mammalian and to make it discover efficiently as a vector used for recombination vector production, it is desirable to use a virus vector. As a virus vector, the Adenoviridae, Retroviridae, The Parvoviridae, the department of a Herpes virus, the Poxviridae, the department of papovavirus, The department of a HEPADONA virus, Togaviridae, the department of a FURABI virus, the Coronaviridae, Rhabdoviridae, Paramyxoviridae, the Orthomyxoviridae, The vector which originates from the viruses belonging to one ** of the groups which consist of the department of a BANYA virus, Arenaviridae, and Reoviridae, and these viruses, Adenovirus dodeca HEDORON vector [Fender et al., Nature Biotech.15 : The vector originating in virus protein like 52 (1997)], Although the vectors (for example, Sendai Virus, a liposome vector, etc.) which combined virus protein with liposome are included, human adenovirus is used preferably.
[0013] For example, the example of the approach of improving the symptoms

of a patient with these symptoms is shown below, using adenovirus as a vector.
(i) As for the construction recombination cosmid of the recombination cosmid containing the KUROSO gene cDNA, it is desirable that 5 mold adenovirus genomic DNA which carried out deletion of E1A, E1B, and E3 further is included including a promotor, the KUROSO gene cDNA, and a poly A addition signal.
[0014] pAxCAwt [Nucl.AcidsRes., 23, and 3816 (1995)] etc. is raised as cosmid for introducing the KUROSO gene cDNA. Although all can be used if it is DNA indicated by WO 98/29544 as a KUROSO gene cDNA, it is not limited to these. DNA which has the base sequence chosen from the base sequence expressed with the array numbers 1, 2, 3, 4, and 5 as a concrete array, this DNA, DNA hybridized under stringent conditions, etc. is raised.
[0015] With DNA which can be hybridized under stringent conditions here DNA which has the base sequence expressed with either of the array numbers 1-5 is used as a probe. DNA obtained by using a colony hybridization method, a plaque hybridization method, or a Southern blotting hybridization method is meant. The filter which fixed DNA of a colony or the plaque origin is specifically used. The SSC solution of 0.1 - 2 double concentration the bottom of the sodium chloride existence of 0.7-1.0M, and after performing hybridization at 65 degrees C (the presentation of the SSC solution of concentration 1 time) DNA which can be identified by washing a filter under 65-degree-C conditions can be raised using a 150mM sodium chloride and 15mM sodium-citrate twist. Hybridization is the 2nd edition of molecular cloning, current PUROTO call Inn molecular biology, and DNA Cloning 1. : According to the approach indicated (1995), it can carry out to Core Techniques, A Practical Approach, Second Edition, Oxford University, etc. When it calculates using FAST as DNA which can be hybridized, specifically, the base sequence expressed with the array numbers 1, 2, 3, 4, and 5, DNA which has at least 60% or more of homology, DNA which has 80% or more of homology preferably, and DNA which has 95% or more of homology still more preferably can be raised.
[0016] In addition, especially many actuation of dealing with phage, a plasmid, DNA, various enzymes, Escherichia coli, a cultured cell, etc. was performed to the volumes Molecular Cloning, A Laboratory Manual, and on T.Maniatis, the 2nd edition (1989), and Cold Spring Harbor Laboratory (it abbreviates to the 2nd edition of molecular clo NINGU hereafter) according to the approach of a publication, unless it refused. With a conventional method, cosmid is cut with a suitable restriction enzyme, for example, SwaI etc., it rearranges by connecting the KUROSO gene cDNA, and cosmid is produced.
(ii) Production of the production recombination adenovirus of the recombination adenovirus containing the KUROSO gene cDNA is producible

by the approach [Proc.Natl.Acad.Sci.USA, 93, and 1320 (1996)] of Miyake and others.

[0017] With the recombination cosmid containing the KUROSO gene cDNA specifically created by (i), for example, E3, E1A which were cut by EcoT22I, 5 mold adenovirus Ad5dIXDNA [J.Virology, 54, and 711 (1985)] which suffered a loss in E1B is mixed. A calcium phosphate method and the RIPOFE cushion method [JP,2-227075,A and experimental-medicine separate volume new gene engineering handbook Yodosha (19996)] are used. For example, E1A, It introduces into the cell strain containing an E1B gene, for example, Homo sapiens embryo origin 293 cell, [J.Gen.Virol., 36, and 59 (1977)]. If recombination of cosmid and Adenovirus DNA arises in intracellular, in order that recombination adenovirus may generate and extinction of a cell may start, generation of the recombination adenovirus which includes extinction of this cell for the KUROSO gene cDNA in an index is checked. The recombination adenovirus solution which crushes a cell and contains the KUROSO gene cDNA is obtained by collecting the cells which became extinct, for example, repeating and performing freeze thawing or using cell homogenizer.

[0018] It rearranges from the obtained solution, and DNA of adenovirus is extracted with a conventional method and the structure is checked by cutting with a restriction enzyme, for example, XhoI.

(iii) DNA of the purification profit **** recombination adenovirus of recombination adenovirus follows Kanegae's and others approach [Jpn.J.Med.Sci.Biol., 47, and 157 (1994)]. 2 times of cesium chloride density gradients refine, and with solutions, such as PBS which contains glycerol 10%, HEPES-MgCl2 which contains glycerol 10%, and HEPES-EDTA which contains glycerol 10%, it can save at -80 degrees C after suspension, and can be used suitably.

(iv) Dialysis processing of the recombination virus solution which discovers the KUROSO gene cDNA obtained by administration (iii) to the symptoms model of the recombination adenovirus containing the KUROSO gene cDNA is carried out, glycerol is removed, it dilutes and rearranges in optimum dose using a physiological saline, and a virus is obtained. By intramuscular injection, the Otsuka Long-Evans Tokushima Fatty (OLETF) rat [Diabetes, 41, and 1422 (1992)] (30 weeks old) which shows the symptoms which produced hypertension and hyperlipidemia with obesity and the high insulinemia, and were similar to Homo sapiens NIDDM of the endomorph (non-insulin dependent diabetes mellitus) is medicated with recombination virus 5X108pfu for three weeks once per week, and it checks to it whether the symptoms which a symptoms model shows have had an improvement in the progress after administration. Although the example of this invention approach of using adenovirus was shown, the above can use any virus, if the

object of this invention except adenovirus can be attained.
[0019] Production of the recombination virus vector using other virus vectors can be performed by replacing the coding region of the virus protein which corresponds so that the code of the KUROSO protein may be carried out using a general recombinant DNA creation technique (see the 2nd edition of the molecular cloning etc.) to DNA which carries out the code of the protein which constitutes a virus. About production of cosmid or the extract of DNA, and other gene modification technology, it can carry out, for example to the following reference by the approach of a publication.
[0020] Wolff ed., Gene therapeutics: Methods and-applications-of direct genetransfer. Birkhaeuser, Boston, 1994; Kaplitt and Loewy eds., Viral vectors: Gene therapy-and-neuroscience applications. Academic Press, San Diego, 1995; Liu et al. eds., DNA vaccines: A new era in vaccinology.Annals of the New York Academy of Sciences vol.772. The New York Academy ofSciences and New York, 1995; Gluzman and Hughes eds. and Viral vectors: Current communications in molecular biology Cold Spring Harbor Laboratory and New York, 1988;Roth ed. and Methods The remedy constituent containing in cell biology.vol.43.Protein expression in animal cells.Academic Press and a San Diego 1994. recombination vector Although this vector independent is possible, it is desirable to provide as remedy pharmaceutical preparation manufactured by the approach of arbitration which usually mixes this vector together with one or the support beyond it permitted in pharmacology, and is used in the technical field of galenical pharmacy. The sterility-solution which dissolved in aquosity support, such as water solutions, such as water or salt, a glycine, a glucose, and Homo sapiens albumin, preferably is used. Moreover, a sodium chloride, the additive permitted in pharmacology, for example, the sodium acetate, like the buffer-ized agent for bringing a pharmaceutical preparation solution close to physiological conditions or an isotonizing agent, sodium lactate, potassium chloride, a sodium citrate, etc. can also be added. Moreover, it freeze-dries, and it can store, it can be made to be able to dissolve in a solvent suitable at the time of an activity, and can also use.
[0021] As for a route of administration, it is desirable to use the most effective thing on the occasion of a therapy, and the parenteral administration in hypodermically, intramuscular, and a vein etc. can be raised in internal use or the oral cavity, a respiratory tract, and the rectum. As an administration gestalt, a spray, a capsule, a tablet, a granule, syrups, an emulsion, a suppository, injections, ointment, a tape, etc. are raised. As suitable pharmaceutical preparation for internal use, an emulsion, syrups, a capsule, a tablet, powder, a granule, etc. are raised. For example, a liquid preparation object like an emulsion and syrups can be manufactured, using flavors, such as antiseptics, such as oil, such as glycols, such as saccharides,

such as water, cane sugar, a sorbitol, and fruit sugar, a polyethylene glycol, and propylene glycol, sesame oil, olive oil, and soybean oil, and p-hydroxy benzoate ester, a strawberry flavor, and peppermint, as an additive. A capsule, a tablet, powder, a granule, etc. can be manufactured using plasticizers, such as surfactants, such as binders, such as lubricant, such as disintegrator, such as excipients, such as a lactose, grape sugar, cane sugar, and a mannitol, starch, and sodium alginate, magnesium stearate, and talc, polyvinyl alcohol, hydroxypropylcellulose, and gelatin, and fatty acid ester, and a glycerol, etc. as an additive.

[0022] Injections, a suppository, a spray, etc. are raised as suitable pharmaceutical preparation for parenteral administration. For example, injections are prepared using the support which consists of salting in liquid, a grape-sugar solution, or both mixture. A suppository is prepared using support, such as cacao butter, a hydrogenation fat, or a carboxylic acid. Moreover, a spray is prepared using the support which the oral cavity and respiratory tract membrane of the vector itself [this] or a recipient are not stimulated [support], and distributes this vector as a detailed particle, and makes absorption easy. A lactose, a glycerol, etc. are specifically illustrated as support. By the property of this vector and the support to be used, pharmaceutical preparation, such as aerosol and dry powder, is possible. Moreover, the component illustrated as an additive by the oral agent also in these parenteral agents can also be added. Although a dose or the count of administration changes with classes of the curative effect made into the object, a medication method, a therapy period, age, weight, and virus vector etc., it usually prescribes 103-1015 pieces for the patient as a virus vector per adult. In this invention, a disease can also be treated by medicating a patient with the KUROSO gene cDNA using the approach of gene therapy. The effectiveness at the time of treating symptoms evaluates lowering of blood pressure, and an improvement of a blood vessel inner-bark function against an index using the above approach. As the general approach which measures the function of a blood vessel inner bark, the method of investigating the vasodilatation reaction of an inner-bark dependency is raised. This is ****** 189 of [medicine which is the approach medicate an artery with an inner-bark dependency vasodilator like acetylcholine, and extent of the vasodilatation in that case estimates NO secretion ability of an inner bark, and 517(1999)].

[0023] Hypertension and hyperlipidemia are hereafter produced with obesity and the high insulinemia as a virus vector, using the mouse origin KUROSO gene cDNA as a gene incorporating the adenovirus (Ad5) of Homo sapiens 5 mold, and although this invention is concretely explained using the example which has improved the blood vessel inner-bark function of the Otsuka Long-Evans Tokushima Fatty (OLETF) rat which shows symptoms similar to

Homo sapiens NIDDM of the endomorph, this invention is not limited to these examples.

[0024]

[Example] Example 1: The blood vessel functional improvement by the recombination adenovirus administration containing the KUROSO gene cDNA.

(Process 1) Production of the recombination adenovirus containing the mouse origin KUROSO gene cDNA followed the approach [Proc.Natl Acad.Sci.USA., 93, and 1320 (1996)] of Miyake and others fundamentally. Both ends were graduated for the 3.1kb fragment which cuts the plasmid pNKM101 (FERM BP-5765, WO 98/29544) which specifically contains the mouse origin KUROSO gene cDNA by NotI and XbaI, and contains this obtained gene by DNA Blunting kit (TAKARA SHUZO CO., LTD. make).

[0025] g, E3, and 1micro of E1 SwaI fragments g of the cosmid pAxCAwt [Kanegae Nucl(s).Acids Res., 23, and 3816 (1995)] including the chimera promotor (CAG promotor) of 5 mold adenovirus genome which carried out deletion of A and the E1 area B and a cytomegalovirus enhancer, and a chicken beta actin promotor were dissolved in 20micro of T4 DNA ligase buffer solutions I 3micro of these fragments, and the ligation reaction was performed for T4 DNA ligase in this solution at 1 unit **** and 16 degrees C for 18 hours.

[0026] The in-vitro packaging (inch vitro packaging) was performed using this ligase reaction mixture and Gigapack II XL Packaging Extract (product made from Stratagene), the obtained phage was infected to Escherichia coli DH5alpha [J.Bacteriology, 170, and 611 (1988)], and recombination cosmid was acquired. In addition, the check of the direction to the promotor of the mouse origin KUROSO gene cDNA in recombination cosmid is BamHI about cosmid. It carried out by detecting the fragment of 1.6kb after cutting.

[0027] Thus, E3 cut by obtained cosmid 8microg and EcoT22I, E1A, and 5 mold adenovirus Ad5dIXDNA[J.Virology., 54, and 711] (1985) 1microg which suffered a loss in E1B were mixed, and transfection was performed to Homo sapiens embryo origin 293 cell by the calcium phosphate method using CellPhect Transfection Kit (product made from Pharmacia Biotech). According to Kanegae's and others approach [biotechnology manual series, 4, 43-58, and Yodosha (1994)], a recombination virus was acquired henceforth.

[0028] According to Kanegae's and others approach [Jpn.J.Med.Sci.Biol., 47, and 157 (1994)], 2 times of cesium chloride density gradients refined this recombination virus, and by PBS which contains glycerol 10%, after suspension, it saved at -80 degrees C, and was used suitably. When the virus titer of this recombination virus solution was calculated according to Kanegae's and others approach [Jpn.J.Med.Sci.Biol., 47, and 157 (1994)], it turned out that a 1X109 pfu/ml virus is included.

[0029] (Process 2) The recombination virus which was obtained at the process 1 and which rearranges, carries out dialysis processing of the virus solution, removes glycerol, dilutes in optimum dose using a physiological saline, and discovers mouse overall-length mold KUROSO was obtained. Hypertension and hyperlipidemia were produced with obesity and the high insulinemia, and the Otsuka Long-Evans Tokushima Fatty (OLETF) rat [Diabetes, 41, and 1422 (1992)] (30 weeks old) which shows symptoms similar to Homo sapiens NIDDM of the endomorph was medicated with recombination virus 5X108pfu for three weeks once per week by intramuscular injection. Consequently, that whose blood pressure of a rat was 156.3**4mmHg (n= 8) by the group non-prescribing a medicine for the patient has been improved by 139.4**7mmHg (n= 5) in an administration group.

[0030] (Process 3) Sodium pentobarbital (50 mg/kg) is injected intraperitoneally to the OLETF rat obtained at the process 2, after anesthesia, a thorax is cut open and a thorax main artery is extracted (3mm). The isolated thorax main artery (main artery ring) is applied between two steel wires, and this is dipped in a 10ml Krebs' bicarbonate solution [120mM NaCl, 5.2mM KCl, 2.4mMCaCl2, 1.2mM MgSO4.7H2O, 25mM NaHCO3, 0.03mM Na2-EDTA, 11mM dextrose (pH7.4)]. The solution has saturated oxygen through the air bubbles of 95% of oxygen, and 5% carbon dioxide. It fixes and one edge of a wire is connected to a dynamics converter Biochem.Biophys.Res.Commun., 248, and 324 (1998) according to the approach of a publication at another edge. After adding 2.0g weight to a main artery ring, applying tension and leaving it for 90 minutes, the norepinephrine of 0.1microM is added and it is made to contract. When acetylcholine with a last concentration [M] of 10micro is added in this solution, what% of the contracted die length evaluates an inner-bark function by whether it loosened and recovered. (OLETF) The rate of relaxation of the main artery ring prepared after prescribing for the patient the adenovirus which discovers mouse overall-length mold KUROSO by which a code is carried out to a rat (30 weeks old) by DNA which has the base sequence expressed with the array number 3 by intramuscular injection for three weeks once per week was 83**3%. On the other hand, by the OLETF rat non-taken a measure, the distinct improvement was found at 67**2%.

[0031]

[Effect of the Invention] Becoming that the therapy of the symptoms in which a blood vessel inner-bark function is improved, arteriosclerosis and hypertension are begun, and a KUROSO gene participates, or prevention of the onset is possible was shown by by medicating a host with an expression vector including the nucleic-acid array which carries out the code of a therapy or preventives of a disease which are represented by the KUROSO

gene, such as arteriosclerosis and hypertension, by this invention, and carrying into a host DNA with the nucleic-acid array which carries out the code of the remedy.

[0032]

[Layout Table]

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[Translation done.]